TO THE UNITED STATES PATENT OFFICE

In re Application of:
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Title: TOPICAL COMPOSITION IN THE FORM OF A GEL FOR TREATING SKIN BURNS

DECLARATION OF HAROLD ARMANDO GOMEZ TORRES, MD
37 C.F.R. § 1132

I, Harold Armando Gomez Torres, hereby declare as follows:

1) My name is Harold Armando Gomez Torres
2) I am the inventor of this application
3) Several studies have been carried out in order to determine the improved therapeutic effect of the composition claimed in this application, namely, a topical composition in the form of a gel for treating patients with superficial skin lesions and burns. More particularly, the present invention relates to two barrier gels, one of carboxymethylcellulose (CMC) and the other of Carboxymethylene Carbopol that allow for obtaining a single gel designed for the therapeutic treatment of patients with skin lesions, offering them a protective and isolating barrier effect for the burns or abrasions. This concept, in addition to the qualities of papain and to the properties of drugs such as lidocaine and chlorhexidine, offers novel and ideal therapeutic elements for the management of skin lesions. Therefore,

the claimed composition provides barrier, antiseptic, debriding, analgesic, and anti-inflammatory effects.

4) The barrier effect of the composition is obtained through the combination of the two said gels. Rheological tests were conducted on three different samples in order to illustrate this concept: i) CMC and papain gel; ii) carbopol and papain gel y, iii) CMC, carbopol, and papain gel, all of them according to the invention. The tests were performed by the laboratory CECOLTEC LTDA. (Annex report of September 20th 2010). Using oscillation tests (with a rheometer, as indicated in more detail in the study report) the applicability, stability of storage, and appropriate viscosity of the samples were all demonstrated, thus giving a strong foundation for the formulation and quality control of the claimed composition. The tests conducted with the gels were Yield Stress Test and Frequency Sweep Test.

5) According to the viscosity curve, the product with the most difficulties for application was found to be CARBOPOL + PAPAIN. This can be seen in Figures 2 and 3, where the flow curve and cession strength denote the said characteristic. For a manually applied skin product (i.e., one for which no special applicator or similar is used), substances with a much lower cession strength are needed in order to obtain a better "spread" of the product. The above may be similarly confirmed through the amplitude scan of the sample in an oscillation test. The "resistance" of the microstructure is given by two factors: The magnitude of the elastic modulus (Figure 4, Red lines, Y axis) or G', and the percentage of displacement (strain) needed to "break down" the said structure (X axis), as determined by the magnitude of the

"plateau". However, the CMC + PAPAIN sample shows a much lower elastic modulus (that is, a greater ease of application), whereas the CMC + CARBOPOL + PAPAIN sample shows a smaller linear viscoelastic region (LVER) (magnitude of the "plateau"), ideal for an easier release of the active ingredient in the said structure.

6) On the other hand, using the frequency sweep test, the likelihood of destabilization of the product due to low-frequency effects (possible sedimentation effects at rest or a shortened "shelf life" of the product) are demonstrated because at some point the viscous modulus would become greater than the elastic modulus (blue lines and red lines, G' and G'' respectively), thus indicating a poor likelihood of "recovery" of the sample. The CMC + PAPAIN sample shows this feature, and thus a potential "phase separation" can be predicted (if there are any such phases), or simply a potential separation of the active compound atop the vehicle.

- See Annex 1 (Applications Report on Rheological Measurements of CMC + PAPAIN; CARBOPOL + PAPAIN; CMC + CARBOPOL + PAPAIN)

7) Preparation of the invention. The gel according to the invention cannot be obtained by merely mixing up the components, as taught by the prior art. In fact, the gel according to the invention requires that each one of the barrier gels is prepared before mixing. To illustrate this concept, HUMAX PHARMACEUTICAL LABORATORY was requested to conduct an experiment to prepare the final gel of the invention in a single step and in two different ways: At high temperature with all of the components (according to the

prior art) and at low temperature with all of the components (according to the prior art).

8) The first situation, (i.e., at high temperature with all of the components) yields a yellow compound resulting from oxidation that lacks the physicochemical properties needed for the intended use, because the interfacial charges of both CMC and Carbopol are different.

9) In the second situation (i.e., at low temperature with all of the components) the mixture cannot be obtained, because the CMC does not fully dissolve at low temperature because it is mixed with Carbopol; this substance becomes hydrated more quickly than CMC, resulting in the persistence of undissolved CMC particles that form a precipitate.

(The final result can be observed in the document identified as Annex 3 issued by Humax Pharmaceutical and signed by Ms. Alba Ceballos, Pharmaceutical Chemist)

10) Based on the above, in order to obtain the resulting gel according to the invention it is necessary to prepare the carbopol gel at low temperature, the CMC gel at high temperature, and then the two gels are mixed and the active principles are added. The resulting gel exhibits optimum viscosity and cadence features for application over the skin.

11) Rheological tests could only be conducted for the gel prepared at high temperature with all of the components at the same time. The gel prepared according to the invention (i.e., with the two barrier gels being prepared separately and then mixed) is found to have a greater stability than the

gel prepared according to the prior art (i.e., with all of the components mixed at the same time).

- See annex 2 (Applications Report on Rheological Measurements of CMC + CARBOPOL + PAPAIN; CMC + CARBOPOL + PAPAIN (according to the prior art))

12) On the other hand, surface tension tests were run to demonstrate that the composition according to the invention (including lidocaine and chlorhexidine) does not lose surface tension, and thus remains properly applied on the skin, (samples 12355/56/57/58). These tests were conducted by CALDERON LABORATORIES on October 12th, 2010. The samples included Carbopol gel (carboxymethylene), CMC gel (carboxymethylcellulose), CMC + Carbopol gel (prepared individually and then mixed, according to the invention) and CMC + Carbopol gel + active principles (prepared individually, then mixed, and finally with the active principles added). The surface tension column (dynes/cm) at 20°C showed no relevant variations in the surface tension of the examined gels (72.7 to 62.5).

13) According to the results obtained it can be established that no relevant variation occurred in the surface tension of the composition according to the invention, thus demonstrating its applicability.

(See annexes 4 and 5)

Conclusions:

1. The present invention solves the technical problems posed through its manufacturing process, that is, by obtaining the two gels separately and then mixing them to reach the final composition, as well as by the type of compounds used in the said process.

2. The goals proposed for the final mixture or compositions were reached and demonstrated with the tests and clinical examples included in the dossier.

3. The above deposition demonstrates that the characteristics, preparation, and applicability of the invention are not found in the prior art; thus the novelty and inventive step become manifest.

I hereby declare that all statements made herein based on my own knowledge are true, and that all statements made based on information and belief are believed to be true; moreover, that these statements were made with the knowledge that any willful misrepresentation and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful misrepresentation may jeopardize the validity of the application or any patent issued thereon.

Signs,

Harold Armando Gómez.
c.c.
Inventor